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UNITED STATES DISTRICT COURT
DISTRICT OF OREGON

CALEB HUGGINS,

Plaintiff,

v.

STRYKER CORPORATION, and **STRYKER SALES CORPORATION**, Michigan Corporations; **MCKINLEY MEDICAL, L.L.C.**, a Colorado Corporation; **MOOG, INC.**, a New York Corporation; A**STRAZENECA PLC**, a United Kingdom Corporation; **ASTRAZENECA PHARMACEUTICALS LP**, a Delaware Corporation; **ASTRAZENECA LP**, a Delaware Corporation; and **ZENECA HOLDINGS, INC.**, a Delaware Corporation,

Defendants.

Case No. CV 07-1671 AA

PLAINTIFF'S OPPOSITION TO DEFENDANTS' SUPPLEMENTAL MEMORANDUM IN SUPPORT OF MOTION TO EXCLUDE GENERAL CAUSATION TESTIMONY OF CHARLES BECK, M.D. PURSUANT TO FED. R. EVID. 702 AND FED. R. CIV. P. 37

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I. INTRODUCTION

Defendant Stryker's motion to strike Dr. Beck's testimony boils down to two arguments: First, plaintiffs should be punished with extreme sanctions because Dr. Beck recently discovered the existence of two additional patients who developed chondrolysis after intra-articular placement of a pain pump, only one of which he had not previously disclosed. Stryker demands that Dr. Beck's testimony be stricken under Rule 37 even though Dr. Beck admitted the oversight and promptly offered to – and did – produce the records for those two patients. Second, Stryker argues that Dr. Beck's study is just a case series, and it was so poorly conducted that it fails to meet *Daubert's* exacting standards.

Stryker's first charge – that plaintiffs failed to produce "key data" underlying Dr. Beck's opinion in violation of the Court's orders – is baseless. Plaintiffs did not withhold anything. At his recent deposition, Dr. Beck candidly told Stryker that he discovered that he had inadvertently failed to provide medical records for two patients who were not part of his study. Those records have already been redacted, copied and produced. Dr. Beck did not mean to withhold these records, and plaintiffs' counsel was no more aware of this oversight than Dr. Beck was. The first patient developed chondrolysis *before* she had shoulder surgery by Dr. Beck. Another surgeon had used the pain pump in a previous surgery, not Dr. Beck. And Stryker has had the records of the second patient for many months, before Dr. Beck recently produced them for a second time. There is no "bad faith" conduct or "willful violation" of the Court's order, and it is distressing to plaintiffs and Dr. Beck to defend themselves against such serious accusations. Furthermore, Stryker cannot explain how it is prejudiced by this recent production of two patient files. These records certainly do not undermine Dr. Beck's methodology. They strengthen his conclusions, because they consist of two additional pain pump-related chondrolysis cases.

Stryker's second argument is nothing new. Stryker repeats its previous attacks on Dr. Matsen's study, claiming that because the authors labeled it a "case series," it has no epidemiological value. But regardless of what Stryker wants to call the study, the inescapable fact remains that it was an analysis of two cohorts of patients: those exposed to pain pumps and

those who were not exposed to pain pumps. By classic design, it is a retrospective cohort study. The data sets, which defendants have pretended do not exist, were readily available from the published study. Using the data, two renowned epidemiologists, as well as a team of surgeons and biostatisticians, independently calculated the same risk ratio comparing the two groups. The risk for the pain pump group was astonishingly high, and consistent with the findings in Dr. Matsen's two cohorts.

The thrust of Stryker's attack is not on any errors Dr. Beck might have made in misclassifying chondrolysis cases versus non-chondrolysis cases, or whether a pain pump was put in the joint space or not. Instead, Stryker focuses on minor flaws and limitations. To be sure, Dr. Beck's study has limitations. All studies do. Dr. Beck has acknowledged them in testimony and in his peer-reviewed publication. But none of these criticisms undermine the conclusions he reached. Rather, these limitations simply go to the weight the jury gives the evidence, not its admissibility. Defendants' disagreement with Dr. Beck's conclusions is not a valid reason to exclude his testimony under *Daubert* and Rule 702.

II. ARGUMENT

A. There Is No Factual Basis to Support Stryker's Allegation that Plaintiffs Violated the Court's Order and Are Subject to Sanctions Under Rule 37.

On August 20, 2009, the Court ordered Dr. Beck to produce not only the underlying documents and medical records for the 177 patients in his study, but also the records for all patients who developed chondrolysis after shoulder surgery by Dr. Beck.

Stryker unfairly accuses plaintiffs of withholding what it says are "key data" underlying Dr. Beck's opinion in violation of the Court' order. The so-called deficiencies in his production, which Dr. Beck voluntarily called to Stryker's attention at his recent deposition, consists of just two patients' medical records. Neither of these patients was included in Dr. Beck's 177-patient study. Both patients had intra-articular placement of pain pumps and later developed chondrolysis. As Dr. Beck explained, he only recently discovered that he had not produced the records for these two patients:

> Q: And how recently did you discover, with respect to these two patients you are referring to, that they actually weren't in your study?
>
> A: It was the last two or three months. I mistakenly thought they were actually some of the study patients and it was pointed out to me by my nurse, Elizabeth, that that's not the case. They were outside of the study.
>
> Q: And if you were to receive a request form defense counsel that your records on those two patients and your study notes, which are Exhibit 29, and the list of patient names and corresponding numerical patient identifiers be given to Orange Legal Technologies so they can do proper redactions on those records, and proper placement of the patient identifiers, would you have any objection to that?
>
> A: No. And I would gladly do that as quickly as possible, now that we know where the records are.

Ex. 01, Beck Dep. at 788-789 (Jan. 26, 2010).

Plaintiffs do not dispute that the Court's order dated August 20, 2009 required plaintiffs to produce documents responsive to paragraph 22 of the subpoena of Dr. Beck.[1] As Stryker correctly notes, the request reads as follows:

> Any and all DOCUMENTS and MEDICAL RECORDS relating to any patient of Dr. Beck who developed chondrolysis, arthropathy or other cartilage injury diagnosed after any shoulder procedure ***performed by Dr. Beck***.

Stryker Br. at 9 (emphasis added).

The problem is that Stryker has misinterpreted the scope of its own subpoena. It is clear from the wording of paragraph 22 that Dr. Beck was obligated to produce only those documents relating to patients who developed chondrolysis after surgeries that he – not some other doctor from a different clinic – performed. This distinction is important, as explained below.

1. The first patient's pain pump surgery was not performed by Dr. Beck.

Patient CLB000158, is a woman who was referred to Dr. Beck for a shoulder replacement in June, 2006. She had developed chondrolysis after arthroscopic shoulder surgery

[1] The Court limited the scope of Stryker's subpoena to include only diagnoses of chondrolysis, not "arthropathy or other cartilage injury."

and pain pump use performed in December 2005 by a different surgeon in another hospital, not Dr. Beck. CLB000158-0027-0028. Dr. Beck did not believe he was supposed to produce this patient's records, because she already had chondrolysis before she came to Dr. Beck to perform a shoulder replacement surgery. According to the clear terms of the Court' order and Stryker's subpoena, he was not obligated to do so. As counsel for Stryker explained to the Court, the purpose of the request for records for arthroscopic stabilization procedures for patients not included in the study was to determine whether Dr. Beck was doing anything differently that might cause them to develop chondrolysis. Ex. 02, Hearing Tr. at 25-26 (Aug. 19, 2009). Therefore, arthroscopic procedures done by other surgeons besides Dr. Beck had no relevance to his analysis. Nevertheless, Dr. Beck voluntarily disclosed the existence of this patient to Stryker and promptly produced her records. Stryker simply has no basis to accuse either Dr. Beck or plaintiffs of violating any Court order.

2. The second patient predated Dr. Beck's study.

CLB000159 is a male patient. Dr. Beck performed shoulder surgery on him in February 2003. CLB-000159-0012-0013. Dr. Beck did not previously produce this patient's records because he had mistakenly thought the patient had been included in his published study. Recently, he realized that this patient could not have been included in the study because his surgery predated the study period. Again, Dr. Beck was not required to produce medical records for patients whose surgeries predated August 15, 2003. Ex. 02, Hearing Tr. at 29-33 (Aug. 19, 2009). But once again, Dr. Beck voluntarily disclosed this patient to Stryker and produced his records. Furthermore, Stryker has had this patient's records in its possession for almost two years. The patient filed a lawsuit against Stryker in Utah approximately three years ago, alleging that Stryker's pain pump caused his chondrolysis. Stryker requested and received Dr. Beck's records concerning this patient in April 2008.

In both instances, Dr. Beck was not obligated by any discovery order to produce these two patients' records. But he candidly informed Stryker of their existence, anyway. He immediately produced their files. Dr. Beck has nothing to hide, and neither do plaintiffs.

Moreover, the medical records for these two patients are not "key data underlying Dr. Beck's opinion," as Stryker contends. Nor does Stryker explain how this data vitiates the study results. The existence of records for two additional patients, who both developed chondrolysis after intra-articular exposure to pain pumps, does not undermine the validity of his 177-patient study or his opinion.

In short, there is no substance whatsoever to Stryker's allegations that Dr. Beck or plaintiffs withheld documents in violation of the Court's orders or that they engaged in deliberate bad-faith misconduct. Stryker's motion to strike Dr. Beck's testimony on Rule 37 grounds should be denied.

B. Dr. Beck's Testimony Meets the Threshold for Admissibility under *Daubert* and Rule 702.

In its latest effort to disqualify Dr. Beck as an expert, Stryker repeats its mantra that the Hansen/Beck paper is nothing more than a case series – and a bad one at that – and has no scientific value. Therefore, Stryker intones, Dr. Beck's testimony must be discarded in its entirety. In support of its argument, Stryker unfairly distorts Dr. Beck's statements and exaggerates what it perceives as flaws in Dr. Beck's analysis. But the perfection that Stryker demands is not what *Daubert* requires.

The standard for admissibility of expert testimony is a showing that the methodology followed by the expert in reaching his conclusions was scientific. Stryker forgets that the Hansen/Beck study underwent peer-review before it was published. And since its publication, countless authors have cited the paper with approval. No one in the scientific community has criticized Dr. Beck for publishing his work, and no one has demanded it be retracted. To the contrary, Dr. Beck's groundbreaking study has been well-received by his colleagues in the orthopedic community. Its presentation stimulated a body of laboratory research, which later confirmed that the association Dr. Beck found between pain pumps and chondrolysis was due to the chondrotoxic effects of the continuous infusion of local anesthetics. It is cynical for Stryker

to claim that Dr. Beck's study lacks scientific validity. Dr. Beck's testimony easily meets *Daubert* standards.

1. The Beck/Hansen study, by definition, is a retrospective cohort and contains sufficient data for statistical analysis.

It is true that Dr. Beck submitted his paper to the American Journal of Sports Medicine as a "case series." As Dr. Beck has explained, the reason he did not submit it as a Level II retrospective cohort is because his findings were so alarming that he felt the need to alert the orthopedic community of this condition right away. Ex. 03, Beck Dep. at 449-450. Hiring a biostatistician to compute the odds ratios would delay the study's publication. *Id.*

Stryker, however, persistently maintains that Dr. Beck's study is a case series that lacks a control group. Stryker hopes that if it repeats its mantra often enough, the Court will eventually come to believe it as truth. But the real and inescapable truth is that that by definition, the Beck/Hansen study is a retrospective cohort. Any good textbook on epidemiology will confirm it. In fact, the REFERENCE MANUAL defines cohort studies in detail with a nice diagram. § 340 REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, SECOND at 486, Fig. 1 and Table 1 (Federal Judicial Center 2005). We previously provided quotes and an image of the diagram in our Opposition to Defendants' *Daubert* Motion, filed on October 27, 2009 (Doc. 491).

Dr. Beck's study consists of two "cohorts" of arthroscopic shoulder surgeries. The first cohort is the surgeries in which the shoulder joint space was exposed to a pain pump. The second cohort is the surgeries in which shoulder joint space was not exposed to a pain pump. Another way of putting it is that the "unexposed" cohort served as the control group. Ex. 04, Hansen & Beck (2007) at 5. Twelve of the 19 shoulders, or 63%, in the exposed cohort developed chondrolysis. The study found no chondrolysis in the 158 surgeries in the unexposed cohort. This analysis is described in detail in our October 27, 2009 brief (Doc. 491). Unlike the typical case series, which do not contain a comparison of exposed versus unexposed populations, Dr. Beck's study does.

Drs. Greenland and Wells are not alone in defining the Hansen/Beck study as a retrospective cohort. Recently, Samer Hasan, M.D., Ph.D. and colleagues submitted a Letter to the Editor of the American Journal of Sports Medicine. Ex. 05. They concluded that the study was, indeed, a Level II retrospective cohort and performed their own statistical analysis of the data presented in the study. Hasan et al., like Drs. Greenland and Wells, found an "infinite" odds ratio, which, when computed to a median unbiased estimate of the odds ratio, was 321. They, too, found that the statistical significance of the data made it unlikely that the findings could be due to chance. *Id.* The journal invited Dr. Beck to respond. The analysis by Dr. Hasan et al. and Dr. Beck's response have been accepted for publication and will be published on-line as soon as possible. *Id.*

Of course, even epidemiological studies are susceptible to confounding variables. In his paper, Dr. Beck explained why other potential confounders could not account for such a huge magnitude of risk in his chondrolysis patients. One weakness of the study, which Drs. Beck, Greenland, Wells and Hasan et al. readily acknowledge, is that were no separate analyses of each of the other potential etiological factors. But even so, it was unlikely that any other factor was as probable a cause as chondrolysis because some patients developed chondrolysis without these other factors present. "[T]he 1 consistent factor in every patient with chondrolysis is that all of the patients received intra-articular pain pump catheters that eluted 0.25% bupivacaine and epinephrine, and all were arthroscopic capsular procedures." Ex. 04, Hansen & Beck at 5.

2. Stryker's criticism of the "arbitrary start and end dates" affects the weight, not admissibility, of Dr. Beck's testimony.

Stryker contends that Dr. Beck's study is unreliable because the start and end dates he selected had no scientific connection to when he began using high volume pain pumps in his surgery. As proof, Stryker selectively quotes Dr. Beck's cross-examination. Stryker omitted the more thorough explanation Dr. Beck later gave on direct examination:

> Q: In your prior testimony you mentioned something about records going back to a certain time in electronic format and ability

> to search. But how did you finally arrive at the dates for your published study?
>
> A: What happened during the study period was a change in my practice location that made it very difficult, in terms of records. We were taking records around in boxes and charts. And 12,000 to 15,000 charts is what we were dealing with in my practice alone, and two or three times that with our other partners.
>
> We bought an electronics [sic] medical record system and started scanning them in. This was a point where I noticed the patients coming in with some frequency with chondrolysis around the end of 2003 and early 2004. And so when we decided to look back later in 2004 and early in 2005, we thought that a nice breakoff date, simply for ease of being able to find charts and find records that had already been scanned in, because of patients currently under treatment, would be August 15, 2003. That is the date that I specifically came back and opened my practice at that location. My partners had got in the office first. So that's why there was some confusion. The record system went back to August 1, more or less. The few patients that might have come in prior to that time were later identified, and we just decided not to put them in the study because we didn't want to cloud the dates because it was too hard to go back and sort through the charts. We felt we had enough information.

Ex. 01, Beck Dep. at 778:19-780:7 (Jan. 26, 2010) (Stryker counsel's objections and colloquy omitted).

On direct examination, Dr. Beck explained that he assigned an end date further out from December 2004 in order to capture as much patient data as possible so that he could determine with further assurance whether or not they went on to develop chondrolysis. Neither he nor Dr. Hansen intended to select the beginning and end dates as a way to manipulate the results or findings. "We were simply trying to capture as many patients as we could to sort out what had caused this problem." *Id.* at 780.

There is nothing arbitrary or unscientific about how Dr. Beck went about selecting the beginning date of his study. Defendants raised this criticism with Dr. Greenland, who testified that it is common in research practice to base start dates on the availability of electronic records. Ex. 06, Greenland Dep. at 22:12-22:18 (Rough Feb. 22, 2010). He added, "Research decisions about when to begin a study are often based on the nature of the records,

how expensive it will be to extract information from them, the availability of them and so forth. So that's very common." *Id.* at 22:19-23:4.

Had Dr. Beck used an earlier start date, as Stryker contends he should have, it would only have made the study bigger. It would not have changed the outcome. As Dr. Beck testified, "The only thing that would have changed would possibly be the numbers that were listed, but not the conclusions or the findings that we felt led to the recommendations we made in our conclusions." Ex. 01, at 781.

3. Stryker's assertion that Dr. Beck did not know whether he used only high volume pain pumps is misleading.

Again, Stryker cunningly parses words from Dr. Beck's deposition to suggest that he had no idea whether he used only high-volume pain pumps in his practice after early 2003. Here is what Dr. Beck really said:

> Q: Okay. Doctor, you told us, and I don't want to rehash that, that you started using the 4.0 or 4.16 mL per hour flow rate pumps in early 2003. From the date that you made that first use, did you always use the 4 or 4.16, or was there a period of time that you used some of those and some of the lower flow rate pumps?
>
> A: From what I recall, I ceased using the lower flow rate pumps because I didn't find them effective with the cost. So my supposition is from that point on I would have been using the larger flow and trying it out, if you will.
>
> Q: Okay. So to make sure I understood that correctly, from early 2003, whenever you used your first 4mL pump forward, you would have used only 4 mL pumps.
>
> A: Correct.
>
> Q: There might be one exception here or there, but that's essentially what your recollection is?
>
> A: Correct.

Ex. 01, Beck Dep. at 691:10-692:12 (Jan. 26, 2010).

Dr. Beck's testimony is consistent with the paper he and his colleague published – prior to litigation – which notes, "All affected shoulders had postsurgical intra-articular pain pump catheters (Stryker Instruments, Kalamazoo, Mich) placed in the shoulder with a drip rate

of 4.16 mL/h and filled with 250 mL of 0.25% BH with epinephrine. The patients were told to remove the pain pump catheter from their shoulders 2 days after surgery." Ex. 04, Hansen/Beck (2007). Stryker has produced no evidence from the medical records to refute Dr. Beck's statements, both in his peer-reviewed published paper and in testimony. These attacks on Dr. Beck's credibility are not helpful in assessing the validity of his methodology. At most, they are areas for cross-examination for trial.

4. There is no truth to Stryker's claim that Dr. Beck lacked documentation of intra-articular placement of the catheter.

Stryker also accuses Dr. Beck of guessing whether he placed the pain pump catheter in the intra-articular space of his study patients. Stryker's contention that "there was literally no record of whether the pain pump was placed intra-articularly" is a distortion of Dr. Beck's testimony. His explanation in its entirety reads:

> Q: My question is how would you have determined where the pain pump was placed in those 18 patients? And I'm using that as an example.
>
> A: From the operative report.
>
> Q: Okay. You wouldn't rely on your memory for something like that, would you?
>
> A: It's possible there may have been an occasional case of that if it wasn't specific in the operative report and I had a recollection of the patient. But the information was compiled mostly by Elizabeth and Dr. Hansen.
>
> Q: So for those 11 patients, you would expect that in the op report there would be some description of where the catheter was placed, and it would say bursal or extra-articular?
>
> A: It sometimes did and sometimes didn't. As far as I recall, it did most times.
>
> Q: And when it didn't, how did you ascertain the location of the pump?
>
> A: Based on my practice, what I normally did.
>
> Q: Okay. So there are times where the op report was not specific and you made a decision whether it was extra-articular or intra-articular based on your custom and practice; is that right?

> A: It's possible that happened. I don't recall.
>
> Q: Would that have been the exception rather than the rule or was it common for purposes of these 177 patients that you analyzed?
>
> A: That would have been the exception.
>
> Q: So most of them there would have been an entry in the op report that would specify the location or the placement of the catheter?
>
> A: For most there would be. With different people dictating the record, it was not always consistent.
>
> Q: Okay.
>
> A: And so I had to rely on what I normally know that I do.

Ex. 01, at 687:23-689:7.

Stryker's statement that there was no proof of catheter placement "in a number of patients" is not only an exaggeration; it is pure speculation. Stryker has presented no evidence from Dr. Beck's patient records that this alleged flaw in documentation actually exists, or that it would have changed the outcome of Dr. Beck's analysis. This attack is a hollow one.

5. Stryker's argument that Dr. Beck confirmed only the diagnoses of chondrolysis without confirming non-chondrolysis diagnoses is false and misleading.

One of Stryker's most outrageous assaults on Dr. Beck's methodology is its spurious allegation that he second guessed his "wife's"[2] diagnosis of chondrolysis in patients but failed to follow up on her determinations that that patient did not have chondrolysis. Stryker's misleading sound bites do not tell the whole story. As Dr. Beck explained more fully:

> Q: With respect to Elizabeth Beck filling out study notes and her charts in those study notes, and those are in Exhibit 29, where she filled in whether or not the patient had chondrolysis or not, who was making the determination for your study that you subsequently published as to whether any of these patients suffered chondrolysis or not?

[2] Plaintiffs do not understand the significance of Stryker's references to registered nurse Elizabeth Beck's status as Dr. Beck's "wife," how it affects her professional conduct, or why it is even relevant to Stryker's argument.

> A: All the diagnoses of ***chondrolysis or not*** are made by me. Whatever information she gleaned from the chart, rather than her interpretation, was what she recorded on the chart, on the tables that you are questioning.
>
> Q: So it was you making a diagnosis of chondrolysis, not her?
>
> A: Correct.

Ex. 01, Beck Dep. at 778:2-778:16 (Jan. 26, 2010) (emphasis added). Stryker's insinuation that Dr. Beck admitted having employed different levels of scrutiny in his analysis is absurd, especially given his explicit testimony to the contrary.

C. <u>New Published Research Provides Further Support for Dr. Beck's Findings.</u>

A new retrospective comparison study, published in December 2009 by J. Rapley and colleagues, validates the clinical findings of Dr. Beck. Ex. 07, J. Rapley et al., *Glenohumeral Chondrolysis After Shoulder Arthroscopy Associated With Continuous Bupivacaine Infusion,* 25:12 ARTHROSCOPY: J ARTHROSCOPIC AND RELATED SURG. 1367-73 (Dec. 2009). In this study, the authors investigated all arthroscopic shoulder surgery patients of a single surgeon between 2000 and 2007. The purpose of the study was to measure the incidence rate of chondrolysis when a pain pump is used in the joint space versus in the subacromial space. The study consisted of two qualifying groups of patients with no pre-existing shoulder cartilage abnormalities: 29 patients who had pain pumps inserted in the glenohumeral joint, and 36 patients who had pain pumps inserted in the subacromial space. Of the 29 patients with intra-articular placement of the pump catheter, 13 used a low volume/low flow pain pump, and 16 patients received a high volume/high flow pain pump. A solution of .5% bupivacaine without epinephrine was used in all of the surgeries. At the beginning of the study, the authors hypothesized that chondrolysis is not caused by subacromial use of pain pumps and that chondrolysis was an *uncommon* complication of intra-articular use of pain pumps.

The study found that 19% (3 of 16) of the patients with intra-articular placement of the high volume pain pump developed chondrolysis. *Id.* at 1372. In contrast, <u>none</u> of the patients with the low volume/low flow pain pumps and <u>none</u> of the patients with subacromial placement

developed chondrolysis. This finding surprised the authors. It refuted their hypothesis that chondrolysis was an uncommon complication. They noted, "a 20% incidence of glenohumeral chondrolysis cannot be considered 'uncommon." *Id.*. Notably, these results are similar to the Beck/Hansen study, which found no incidence of chondrolysis in patients who used a low volume pain pump or had the pump catheter placed outside of the joint space. Ex. 04, Hansen and Beck (2007) at 2, 5; Ex. 08, Beck Report at 5. Rapley et al. further observed that the clinical response was related to concentration of the drug and pump volume, and that epinephrine (not used in this study) may worsen the effect. Ex. 07, at 1372. Thus, the higher incidence rate of chondrolysis observed in the Beck/Hansen study compared to the Rapley findings is likely due in part to the use of bupivacaine with epinephrine, as opposed to bupivacaine alone.

D. Dr. Beck's Findings Are Consistent with Other Epidemiological and Laboratory Data, Which, as a Whole, Support an Inference of Causation.

No single item of evidence alone can conclusively establish causation. But "it may serve as one component, that when added to others, does prove causation." *Siharath v. Sandoz Pharms. Corp.*, 131 F. Supp. 2d 1347, 1359 (N.D. Ga. 2001), *citing Joiner v. General Elec. Corp.*, 78 F.3d 524, 531 (11th Cir. 1996), *rev'd on other grounds*, 522 U.S. 136, 146-47 (1997). The Ninth Circuit has repeatedly instructed that the focus of the *Daubert* inquiry must be based on consideration of the evidence as a *whole*, and not in isolation. *United States v. W. R. Grace*, 504 F.3d 745, 765 (9th Cir. 2007); *In re Phenylpropanolamine (PPA) Prods. Liab. Litig.*, 289 F. Supp. 2d at 1242.

This doctrine is not unique to the Ninth Circuit. Courts widely recognize that expert causation testimony is reliable when it is based on the totality of evidence. *See, e.g., In re Seroquel Prods. Liab. Litig.*, No. 6:06-md-1769-Orl-22DAB, 2009 WL 3806435, at *8 (M.D. Fla. Jun. 23, 2009) (finding that expert's reliance on a combination of epidemiological studies, animal studies, case reports, and analogy to similar drugs as "confirmatory pieces of the totality of the evidence" satisfied *Daubert*); *In re Stand 'N Seal Prods. Liab. Litig.*, 623 F. Supp. 2d 1355, 1374 (N.D. Fla. 2009) (expert did not rely on case reports alone for his opinion, but also

his personal clinical experience with the toxin, therefore, his testimony was admissible); *McCarrell v. Hoffman-La Roche, Inc.*, 2009 WL 614484, at *27 (N.J. Super. App. Div. Mar. 12, 2009) (upholding the admissibility of expert's testimony based on a combination of case reports, peer-reviewed journals, animal studies, a pre-clinical human study and a biologically plausible explanation); *In re Neurontin Marketing Sales Practices, and Prods. Liab. Litig.*, 612 F. Supp. 2d 116, 158-59 (D. Mass. 2009) (finding plaintiffs' experts general causation opinions admissible based on an FDA meta-analysis, case report data, animal studies, *in vitro* studies and adverse event report data).

The Supreme Court of Kentucky recently upheld the trial court's ruling admitting the testimony of plaintiffs' experts in a case in which the plaintiff alleged that the post-partum drug Parlodel caused the decedent to suffer a fatal seizure. *Hyman & Armstrong, P.S.C. v. Gunderson*, 279 S.W. 3d 93 (Sup. Ct. Ky. 2008), *reh'g denied* (Apr. 23, 2009). The trial court had found that the combination of case reports, adverse event reports, animal studies and chemical analogies, articles in medical textbooks and scientific publications was a sufficient foundation for the experts to base their opinions. Applying the *Daubert* criteria, the court found that each of the pieces of evidence was derived from recognized scientific methodologies:

> We agree with the trial court's assessment that although the individual pieces of evidence may not conclusively prove general causation, together they tend to show that Parolodel can cause postpartum seizures in women taking the drug for PLLS.

Id. at 106.

In this litigation, for instance, defendants have vigorously attacked Dr. Beck's study, dismissing it as a "collection of case reports" and thus lacking in scientific validity. In addition, defendants discredit plaintiffs' experts for deriving their opinions on causation by collecting and reviewing individual studies and epidemiological data. This "totality of the evidence theory" for reaching causal inferences, they proclaim, is "not a methodology at all." Ex. 09, *McClellan et al.*, Hearing Tr. at 36:24-37:6 (Nov. 17, 2009). Defendants also fault plaintiffs' experts for reading published studies. But as any scholar will tell you, it is unscientific to ignore the totality

of the data. Scientists do not look at a particular piece of the evidence puzzle in isolation and disregard the rest. The scientific method requires an expert to look at all of the best available evidence and, in assessing its reliability, make sure that each piece of data is consistent with the others. It is what scientists do every day in making judgments about causation.

One way epidemiologists go about reaching causal inferences is to employ a set of guidelines known as the "Bradford Hill" considerations. A. Bradford Hill, *The Environment and Disease: Association or Causation?*,58 Proc. Royal Soc'y Med. 295 (1965). *See* 375 REFERENCE MANUAL at 526-27. These factors include:

1. Temporal relationship;
2. Strength of the association;
3. Dose-response relationship;
4. Replication of the findings;
5. Biological plausibility (coherence with existing knowledge);
6. Consideration of alternative explanations;
7. Cessation of exposure;
8. Specificity of the association; and
9. Consistency with other knowledge.

Id. at 527.

Several courts have found these guidelines useful in assessing the reliability of causation testimony based on associations from epidemiological studies. *See In Re Viagra Prods. Liab. Litig.*, 572 F. Supp. 2d 1071, 1081 (D. Minn. 2008). Although each of the Bradford Hill factors is important, the Reference Manual cautions, "One or more of these factors may be absent even when a true causation relationship exists." 375 REFERENCE MANUAL at 527. Thus, a *Daubert* motion should not be granted on the grounds that the evidence fails to satisfy each of the Bradford Hill criteria. *In Re Viagra*, 572 F. Supp. at 1081.

E. The Bradford Hill Considerations Demonstrate that Dr. Beck's Analysis Supports a Causal Relationship Between Pain Pumps and Chondrolysis

Dr. Beck's study found a strong association between the intra-articular placement of pain pumps and chondrolysis. Nevertheless, defendants' mantra in the course of this litigation has been is that "association is not causation." The Bradford Hill factors are helpful in establishing that Dr. Beck's analysis is reliable and supports his general causation testimony.

1. Temporal Relationship

A temporal relationship is a necessary prerequisite for causation to exist. That is, if an exposure causes disease, it must occur before the disease develops. 376 REFERENCE MANUAL at 528. All of Dr. Beck's patients (as well as Dr. Matsen's patients) developed chondrolysis after pain pumps were used in their shoulder joints. Therefore, a temporal relationship exists.

2. Strength of the Association

As the REFERENCE MANUAL notes, relative risk or risk ratio is one of the "cornerstones" for causal inferences. *Id.* The higher the relative risk is, the more likely it is that an association is causal. *Id.* Dr. Beck's study found that 63% of his patients who had intra-articular placement of high volume pain pumps developed chondrolysis, while 0% of his patients with no exposure to pain pumps developed chondrolysis. Drs. Greenland and Wells, both preeminent epidemiologists, calculated the relative risk revealed by the data from Dr. Beck's study. Using generally accepted statistical methods, they found a stunningly high median unbiased estimated odds ratio of 321. The analysis by Dr. Hasan's team made the same finding. Ex. 10, Greenland Report at 6; Ex. 11, Wells Report at ¶ 8. It is a larger association than Dr. Greenland has ever seen in his entire career. For comparison, the association between a lifetime of smoking a pack of cigarettes per day and lung cancer is around 10. Ex. 10, Greenland Report at 7. This extremely high relative risk is compelling evidence that the strength of the association between intra-articular use of pain pumps and chondrolysis is enormous.

3. Dose-Response Relationship

A dose-response relationship means that the higher the dose or intensity of the exposure is, the greater the harm. 377 REFERENCE MANUAL at 529. I n this case, the laboratory studies by Dr. Chu and others demonstrated that prolonged exposure of human and bovine joint cartilage to bupivacaine and other local anesthetics is chondrotoxic at doses ranging from 0.25 to 0.5%. The toxicity increased with both dose and duration. *See* Ex. 12, Chu et al. (2008). This dose- and duration-response relationship has been repeated with similar results in other studies. The presence of a strong-dose response relationship between continuous infusion of anesthetic drugs through a pain pump catheter and chondrolysis provides additional support for causation.

4. Replication of the Findings

A study has heightened validity if it is replicated in different populations and by different investigators. 377 REFERENCE MANUAL at 531. Here, the retrospective studies of Dr. Matsen and Dr. Rapley replicate the findings Dr. Beck made in his patient population. Like Dr. Beck's study, Dr. Matsen's study of 396 shoulder surgery patients contained two cohorts. Forty-two percent of the exposed group (patients with intra-articular pain pumps) developed chondrolysis, while there were no cases of chondrolysis in the unexposed group (patients who did not receive a pain pump). Drs. Greenland and Wells calculated a median unbiased estimated odds ratio of 282 for the exposed versus unexposed group. Like Dr. Beck's study, the odds ratio in Dr. Matsen's study is enormous. Similarly, in Dr. Rapley's two cohorts, 19% of the patients with intra-articular placement of the high volume pain pump developed chondrolysis. In contrast, none of the patients with the low volume/low flow pain pumps and none of the patients with subacromial placement (outside the joint space) developed chondrolysis. All three studies replicated the results of the others, using different populations and different investigators. These findings support a causal relationship.

5. Biological Plausibility

Biological plausibility is a difficult factor to assess because it depends upon knowledge of the mechanisms by which the disease develops. 378 REFERENCE MANUAL at 532.

Researchers are not certain of how, precisely, the anesthetics in the pain pump damage the cartilage. Existing studies show that bupivacaine with epinephrine is more chondrotoxic than bupivacaine alone. Scientists are still studying the disease process on the cellular and subcellular level. But the *in vitro* and animal studies provide convincing evidence that local anesthetics have a toxic effect by some means on joint cartilage.

6. Consideration of Alternative Explanations

Dr. Beck's and Dr. Matsen's studies did consider alternative explanations for the high incidence of chondrolysis in their patients who received pain pumps. They accounted for those alternative factors in their studies and concluded that pain pumps were by far the strongest and most likely explanation for the relationship.

7. Cessation of Exposure

When cessation data is available and eliminating exposure reduces the incidence of disease, "this factor strongly supports a causal relationship." *Id.* at 534. Dr. Beck reported that in his patient population, when he quit using high volume pain pumps in the joint space, he never observed a single case of chondrolysis. Ex. 04, Hansen/Beck (2007). Similarly, after Dr. Benz discontinued using pain pumps in the intra-articular space, there were no further cases of chondrolysis in his patients. Ex. 13, *Grossnickle* Tr. at 1636 (March 5, 2009).

8. Specificity of the Association

Unlike diseases like lung cancer, which have multiple causes, there are relatively few causes of sudden onset chondrolysis in younger, otherwise healthy people. Chondrolysis of the shoulder was practically unheard of before the advent of arthroscopic shoulder surgery. In Dr. Beck's practice, he never saw a single case of chondrolysis before he started using high-volume pain pumps in the shoulder joint space, even though he used radiofrequency devices, bioabsorbable sutures and suture anchors, which have also been associated with chondrolysis. Although there are other causes of chondrolysis besides intra-articular use of pain pumps, the association is more specifically and frequently related to pain pumps than any other factor.

9. Consistency with Other Knowledge

There is no population "trend" study to determine and compare the rise and fall in shoulder chondrolysis rates with the rise and fall in pain pump sales. Such a study would be difficult to conduct because pain pumps are used for other surgical procedures besides arthroscopic shoulder surgeries. In addition, some surgeons have continued to use pain pumps for shoulder arthroscopic surgeries, but *not* in the joint space based on studies such as Rapley et al., which show no increased risk of chondrolysis in patients who received pain pumps in the subacromial space.

An analysis of the Bradford Hill factors, when viewed in the aggregate, provide a "clearer picture of causation." *See In re Seroquel,* 2009 WL 3806435, at *7. Dr. Beck's study is valuable for this reason. Its results stand up well to other sources of evidence. Applying the Bradford Hill criteria provides additional validity for the methodology Dr. Beck used to support his testimony.

III. CONCLUSION

Dr. Beck was the pioneer of the body of knowledge establishing the relationship between intra-articular use of pain pumps and chondrolysis. His study generated further research on the chondrotoxicity of continuous infusion of local anesthetics to cartilage. Dr. Beck's important work led to a change in the standard of care for arthroscopic surgery. As a result, informed orthopedic surgeons no longer use pain pumps in the synovial cavity, thus sparing untold numbers of patients from a crippling and permanent injury. For years, Stryker and other defendants have sought to discredit Dr. Beck and his study. However, his methodology has withstood these attacks. The scientific community continues to recognize the study as a valid and important piece of literature on the question of causation. Only the defendants and their stable of experts reject it. Dr. Beck's testimony meets the threshold for admissibility under *Daubert* and Rule 702.

Accordingly, plaintiffs ask the Court for an order denying Defendants' Supplemental Motion to Exclude the General Causation Testimony of Dr. Charles Beck.

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Respectfully submitted,

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